Pyrimido(4,5-g)quinazoline derivatives with anti-tumour activity.

Patent Number: EP0541404

Publication date: 1993-05-12

Inventor(s): SKIBO EDWARD B (US); LEMUS ROBERT H (US)

Applicant(s):: UNIV ARIZONA (US)

Requested Patent: US5639881

Application Number: EP19920310231 19921109

Priority Number(s): US19910763375 19911108

IPC Classification: A61K31/505 ; C07D487/04

EC Classification: C07D487/04

Equivalents: CA2082297, JP7309873, MX9206438

Abstract

PyrimidoÄ4,5-gÜquinazoline quinone derivatives were synthesized as anthraquinone-like reductive alkylating agents. Like many naturally-occurring antibiotics, these quinone derivatives are designed to afford an alkylating quinone methide species upon reduction and leaving group elimination. Kinetic studies of pyrimidoÄ4,5-gÜquinazoline hydroquinones provided evidence of quinone methide intermediates able to trap nucleophiles (alkylation) and protons. The rate of quinone methide formation is determined by the hydroquinone free energy. Thus, a linear free energy relationship for quinone methide formation was obtained by plotting rates of quinone methide formation, as the log, versus the quinone reduction potential. The pyrimidoÄ4-5-gÜquinazoline quinone methides fall on this free energy plot, showing that these species are formed by the same mechanism as the other structurally-diverse quinone methides previously studied in this research group. A drawback of many quinone antibiotics, particularly the anthracyclines, is the formation of toxic oxygen species by quinone/hydroquinone cycling. In the present invention pyrimidoÄ4,5-gÜquinazoline hydroquinones are found to be relatively stable toward oxygen, and thus cause little oxygen toxicity. Antitumor screening revealed that the disclosed pyrimid Ä4,5-gÜ quinazoline dione and tetione derivatives possess excellent inhibitory activity against selected human cancer cell lines.

— Please see exhibit 14 —